REMARKS

This Response is to the final Office Action mailed January 11, 2007. Claims 1 to 4, 6 to 8, 13, 15, 16 to 18, 21, 23, 24, 28, 29, 32 and 40 are pending. Claims 3, 4, 6 to 8, 13, 15 to 18, 21, 23, 29, 32 and 40 have been canceled herein without prejudice. Applicants maintain the right to prosecute the canceled claims in any related application claiming the benefit of priority of the subject application. Claim 43, which depends from claim 1 has been added. Claim 43 does not raise new issues since it d and merely recites a particular assay to determine formation of inhibitory titers. Accordingly, upon entry of this Response claims 1, 2, 24, 28 and 43 are under consideration.

Regarding the Interview

Applicants wish to thank the Examiner for the Interview held May 11, 2007, during which time the grounds for rejection of record were discussed as well as allowable subject matter. Applicants believe that the amendments herein reflect the subject matter indicated to be allowable.

Regarding Claim 43

New claim 43 is supported, for example, at page 14, lines 11-13; and at page 15, lines 4-6. Thus, as claim 43 is supported by the application, no new matter has been added and entry thereof is respectfully requested.

Regarding the IDS

Two references, namely Snyder *et al.* (Nature Med. 5:64 (1999)) and Herzog *et al.* (Nature Med. 5:56 (1999)), are submitted herewith in an IDS. Applicants note that in both references, the authors report that no inhibitory antibody formation against Factor IX was detected in animals.

I. CLAIM OBJECTIONS

Claims 8 and 17 remain objected to due to the numbering of the claims from which they depend. Claims 8 and 17 have been canceled herein without prejudice. Accordingly, the objection is moot and Applicants respectfully request that the objection be withdrawn.

II. REJECTION UNDER 35 U.S.C. §112, SECOND PARAGRAPH

The rejection of claim 32 under 35 U.S.C. §103(a) as allegedly indefinite is respectfully traversed. The ground for rejection is set forth in the Office Action, pages 3.

Claim 3 has been canceled herein without prejudice. Accordingly, the rejection is moot and Applicants respectfully request withdrawal of the rejection.

III. REJECTIONS UNDER 35 U.S.C. §103(a)

The rejection of claims 13, 15 to 18, 21, 23, 29 and 40 under 35 U.S.C. §103(a) as allegedly unpatentable over Wilson *et al.* (U.S. Patent No. 6,251,957) taken with Conti-Fine (U.S. Patent No. 6,929,796) is respectfully traversed. The grounds for rejection are set forth in the Office Action, pages 3-7.

Claims 13, 15 to 18, 21, 23, 29 and 40 have been canceled herein without prejudice. The rejection will therefore be addressed as it may relate to claims 1, 2, 24, 28 and 43 upon entry of the Response.

In order for a rejection to be proper under 35 U.S.C. §103, *inter alia*, there must have been at the time of the invention 1) a suggestion or motivation to modify or combine the references at the time of the invention; 2) a reasonable expectation of success of producing the claimed invention; and 3) the combined references must teach or suggest each and every claim limitation. Both the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in Applicants' disclosure. See, e.g., *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991) and *In re O'Farrell*, 853 F.2d 894, 903-904 (Fed. Cir. 1988). The prior art must be considered in its entirety....including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540 (Fed. Cir. 1983). In addition, objective evidence of non-obviousness must be considered. *Stratoflex Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538 (Fed. Cir. 1983); *see also*, *In re Corkill*, 711 F.2d 1496 (Fed. Cir. 1985).

Here, *inter alia*, 1) the skilled artisan would not have had a reasonable expectation of success or motivation at the time of the invention in view of the art; and 2) the prior art teach away from the claimed invention. Furthermore, objective evidence of non-obviousness in the form of unexpected results, is submitted herewith.

In terms of a reasonable expectation of success at the time of the invention, as pointed out in the record, the scientific literature is replete with studies in which immune-suppressive agents either failed completely, caused unacceptable adverse side effects, or was limited in duration and effectiveness. Examples include the cited Wilson *et al.* patent who reported that

using CD4 antibodies and CD40L antibodies for immunosuppression did not prevent neutralizing antibodies from forming (column 18, lines 52-56; column 22, Table III; and column 23, lines 22-28). Likewise, in Warrier *et al.* (Blood Coag. Fibrinol. 9(Suppl 1):S125 (1998)), the authors state that "Eradication of the inhibitor by immune tolerance induction (ITI) has only been minimally effective" (page S125, abstract). Furthermore, in Nilsson *et al.* (Proc. Natl. Acad. Sci. USA 83:9169 (1986)), the authors state that "treatment with factor IX and cyclophosphamide was ineffective, resulting in high and persistent anamnestic response." (see page 9173, first sentence under "*Discussion*"). Moreover, in Tengborn (Haemophilia 4:56 (1998)), in 2 patients treated with FIX, cyclophosphamide and gammaglobulin (IV), inhibitory antibodies continued to form with the authors concluding that the treatment had failed (abstract). Additionally, in Fang *et al.* (Human Gene Therapy 6:1039 (1995)), dogs administered FIX and cyclosporin A continued to form anti-adenovirus antibodies (page 1043, Fig. 3). In Trapnell *et al.* (WO 97/39776), neutralizing antibodies formed in mice administered lacZ vector with various immunosuppressive agents (Table 1, pages 36 and 37). Thus, in view of the foregoing, it is clear that the art indicates that immunosuppressive agents frequently fail to reduce or prevent formation of inhibitory antibodies in a wide variety of contexts. Consequently, in view of the art, the skilled artisan would not have had a reasonable expectation of success at the time of the invention.

Moreover, Applicants reiterate that there must have been a motivation to produce the claimed methods at the time of the invention, and that the prior art must be considered in its entirety, including portions that teach away. In this regard, the art is replete with studies indicating the absence of inhibitory antibody formation against proteins delivered by way of gene therapy. Consequently, there would not have been a motivation to produce the claimed methods at the time of the invention.

As set forth in the record, Tripathy *et al.* (Nat. Med. 2:545 (1996)) reported that mice injected with adenovirus harboring human EPO developed anti-EPO antibodies whereas mice injected with adenovirus harboring murine EPO did not develop anti-EPO antibodies. Herzog (Blood 90, part 1, Supp. 1, abstract 1057 (1997))) reported that antibodies against Factor IX following injection with an AAV vector with canine Factor IX into a hemophiliac dog (hemophilia B) were not detected. The fact that both Tripathy *et al.* and Herzog (Blood) report that an immune response was not produced against a protein delivered by way of gene therapy that is the same species as the mammal to which it is delivered means that the skilled artisan would not have been motivated to administer cyclophosphamide prior to or

simultaneously with gene therapy to deliver Factor IX that is the same species as the mammal. Furthermore, in view of the side effects associated with immune suppressive agents, the skilled artisan would have been taught away from administering a drug that is not necessary known to produce side effects.

Previously submitted Exhibits A to D corroborate that human or canine subjects with hemophilia A or hemophilia B, including subjects incapable of producing endogenous Factor IX or Factor VIII, did not produce detectable inhibitors against Factor IX (Exhibits A and B, Manno *et al.*, Blood 101:2963 (2003), and Mount *et al.* Blood 99:2670 (2002), respectively) or Factor VIII (Exhibits C and D, Roth *et al.*, N. Engl. J. Med. 344:1735 (2001), and Powell *et al.*, Blood 102:2038 (2003), respectively). Thus, in view of the absence of inhibitory antibodies the skilled artisan would not have been motivated to administer cyclophosphamide prior to or simultaneously with gene therapy to deliver Factor IX that is the same species as the mammal. Furthermore, in view of the side effects associated with immune suppressive agents, the skilled artisan would have been taught away from administering a drug known to produce side effects- an immune suppressive agent.

As further support that the prior art would not have motivated the skilled artisan, submitted herewith in an IDS are publications by Snyder *et al.* (Nature Med. 5:64 (1999)) and Herzog *et al.* (Nature Med. 5:56 (1999)). Each of the Snyder *et al.* and Herzog *et al.* publications report that no inhibitory antibody formation against Factor IX was detected in animals. Consequently, in view of the absence of inhibitory antibodies against Factor IX and in view of the side effects associated with delivering immune suppressive agents, the skilled artisan would not have had any motivation and would have been taught away from administering cyclophosphamide prior to or simultaneously with gene therapy to deliver Factor IX that is the same species as the mammal.

Finally, Applicants have submitted evidence of unexpected results. Previously submitted Exhibit A was a data summary of 10 dogs treated in accordance with the claimed methods which were followed up to 3.5 years. As discussed, none of the 10 dogs produced detectable inhibitory antibodies against Factor IX up to 39 months after receiving cyclophosphamide with gene therapy. Furthermore, none of the dogs exhibited significant adverse side effects. In contrast, two of three dogs that did not receive cyclophosphamide with Factor IX gene therapy, J62 and E60, produced inhibitory antibodies against FIX.

Accordingly, the claimed methods, which can achieve a long-term reduction or prevention of inhibitory antibodies are in stark contrast to the art of record discussed above.

Consequently, the claimed methods achieve unexpected results in view of the art of record, which constitutes objective evidence of non-obviousness of claims 1, 2, 24, 28 and 43 that must be considered under 35 U.S.C. §103(a).

In sum, in the view of the absence of a reasonable expectation of success at the time of the invention, that the scientific literature is replete with references that would not motivate the skilled artisan to produce the claimed methods, including a number of references that teach away from the claimed invention, and the unexpected results compared to the art of record, claims 1, 2, 24, 28 and 43 would not have been obvious over Wilson *et al.* (U.S. Patent No. 6,251,957) or Conti-Fine (U.S. Patent No. 6,929,796) alone, or in combination, at the time of the invention. Consequently, the rejection under 35 U.S.C. §103(a) is improper and must be withdrawn.

The rejection of claims 1 to 4, 6 to 8, 24 and 28 under 35 U.S.C. §103(a) as allegedly unpatentable over Wilson *et al.* (U.S. Patent No. 6,251,957) taken with Conti-Fine (U.S. Patent No. 6,929,796) and further in view of Trapnell *et al.* (WO 97/39776) is respectfully traversed. The grounds for rejection are set forth in the Office Action, pages 7-9.

Claims 3, 4 and 6 to 8 have been canceled herein without prejudice. The rejection will therefore be addressed as it may relate to claims 1, 2, 24, 28 and 43 upon entry of the Response.

As discussed above and in the record, the scientific literature is replete with studies reporting that immune-suppressive agents either failed completely, caused unacceptable adverse side effects, or was limited in duration and effectiveness. Consequently, in view of the art, the skilled artisan would not have had a reasonable expectation of success at the time of the invention.

As also discussed above and in the record, the scientific literature is replete with studies reporting that subjects incapable of producing endogenous proteins including blood clotting factors (e.g., Factor IX or Factor VIII), did not produce detectable inhibitors against proteins delivered by way of gene therapy, including blood clotting factors (i.e., Factor IX or Factor VIII). Thus, in view of the fact that the art is replete with studies indicating the absence of inhibitory antibody formation against proteins delivered by way of gene therapy the skilled artisan would not have been motivated to administer cyclophosphamide prior to or simultaneously with gene therapy to deliver Factor IX that is the same species as the mammal. Furthermore, in view of the side effects associated with delivering immune

suppressive agents, the skilled artisan would have been taught away from administering cyclophosphamide prior to or simultaneously with gene therapy to deliver Factor IX that is the same species as the mammal.

Finally, previously submitted Exhibit A, a data summary of dogs treated in accordance with the claimed methods which were followed up to 3.5 years, none of whom produced detectable inhibitory antibodies against Factor IX, are evidence of unexpected results. Accordingly, the claimed methods, which can achieve a long-term reduction or prevention of inhibitory antibodies are in stark contrast to the art of record discussed above and in the record. Consequently, the claimed methods achieve unexpected results in view of the art of record, which constitutes objective evidence of non-obviousness of claims 1, 2, 24, 28 and 43 that must be considered under 35 U.S.C. §103(a).

In sum, in the view of the absence of a reasonable expectation of success at the time of the invention, that the literature is replete with references that would not motivate the skilled artisan to produce the claimed methods, that the skilled artisan would have been taught away from the claimed invention, and the unexpected results compared to the art of record, claims 1, 2, 24, 28 and 43 would not have been obvious over Wilson *et al.* (U.S. Patent No. 6,251,957), Conti-Fine (U.S. Patent No. 6,929,796) or Trapnell *et al.* (WO 97/39776) alone, or in combination, at the time of the invention. Consequently, the rejection under 35 U.S.C. §103(a) is improper and must be withdrawn.

CONCLUSION

In summary, for the reasons set forth herein, Applicants maintain that claims 1, 2, 24, 28 and 43 clearly and patentably define the invention, respectfully request that the Examiner reconsider the various grounds set forth in the Office Action, and respectfully request the allowance of the claims which are now pending.

Please charge any fees associated with the submission of this paper to Deposit Account Number 033975. The Commissioner for Patents is also authorized to credit any over payments to the above-referenced Deposit Account.

Respectfully submitted,

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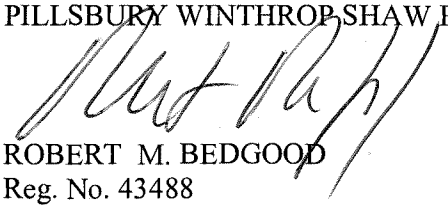

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